



NOTES

MACROCYTIC ANEMIA

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Bone marrow produces larger than normal erythrocytes AKA red blood cells (RBCs)

CAUSES

- **Multifactorial:** nutritional deficits, genetics, substance exposure (e.g. certain drugs, alcohol)

SIGNS & SYMPTOMS

- Fatigue, dyspnea, weight loss, pallor, impaired concentration/memory, diarrhea, onychoschizia (brittle nails)

DIAGNOSIS

LAB RESULTS

- Complete blood count
- Peripheral blood smear analysis
- Blood chemistry
- Iron studies
- Genetic testing

TREATMENT

- Address underlying causes

MEGALOBLASTIC ANEMIA

osms.it/megaloblastic-anemia

PATHOLOGY & CAUSES

- Macrocytic, normochromic anemia characterized by **formation of large RBCs**

CAUSES

Cobalamin and/or folate deficiency

- **Impaired DNA synthesis during erythropoiesis** → uncoordinated maturation of cytoplasm and nuclei in erythroblasts (nuclear-cytoplasmic asynchrony) → abnormally large RBCs (macrocytosis) + defective cells with fragile membranes → RBCs die prematurely → anemia

B₁₂ deficiency

- **Insufficient diet** (e.g. vegan diet without B₁₂ supplements, alcoholism, systemic/mental illness, food insecurity)
- **Malabsorption**
 - **Lack of intrinsic factor** → pernicious anemia
 - **Surgical:** **gastrectomy**, bariatric surgery → lack of absorptive surface → pernicious anemia
 - **Pancreatic insufficiency** → impaired binding of B₁₂ to intrinsic factor → pernicious anemia
 - **Medications that interfere with absorption:** e.g. biguanides, H₂ receptor blockers, proton-pump inhibitors, neomycin

VISIT...

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- Fish tapeworm (*Diphyllobothrium latum*)
→ competes with host for B₁₂

Folate deficiency

- Insufficient diet
- Adequate diet but **increased requirements** (e.g. pregnancy, lactation, chronic hemolysis, exfoliative skin disease)
- Malabsorption (e.g. celiac disease, inflammatory bowel disease, gastric surgery)
- Metabolic interference from medications (e.g. methotrexate, phenytoin, trimethoprim)
- Alcoholism

Less common causes of macrocytosis

- Thiamine-responsive megaloblastic anemia syndrome, congenital anemias (Fanconi anemia, Diamond–Blackfan anemia), myelodysplastic syndromes, pure RBC aplasia, lipid abnormalities (e.g. liver disease), thyroid disease, copper deficiency
- Impaired DNA synthesis also causes formation of giant metamyelocytes → neutrophils with hypersegmented nuclei

SIGNS & SYMPTOMS

- From decreased number of functional RBCs in circulation → decreased RBC oxygen-carrying capacity → tissue hypoxia
 - **Fatigue**
 - **Activity intolerance**
 - **Pallor**
 - **Compensatory mechanisms:** increased heart rate, bounding pulse
- From increased rate of hemolysis, destruction of defective cells
 - **Jaundice:** hemolysis → increased serum bilirubin
 - **Splenomegaly:** increased reticuloendothelial activity secondary to extravascular hemolysis
- **From neuronal demyelination (if B₁₂ decreased): numbness, tingling, weakness,** possible neuropsychiatric symptomatology

DIAGNOSIS

LAB RESULTS

- **Peripheral blood cell analysis**
 - Increased mean corpuscular volume (MCV)
 - Increased mean corpuscular hemoglobin (MCH)
 - Normal mean corpuscular hemoglobin concentration (MCHC)
 - Hypersegmented neutrophils
 - Anisocytosis (different sizes of RBCs)
 - Poikilocytosis (abnormally-shaped RBCs)
 - Macroovalocytes (large oval-shaped cells)
- Decreased RBC count secondary to increased hemolytic destruction of defective erythrocytes
- Decreased reticulocyte count → formation impaired in anemias caused by defective DNA synthesis
- Mild leukopenia and/or thrombocytopenia caused by defective DNA synthesis
- Decreased serum hemoglobin and hematocrit related to decreased number of circulating RBCs
- Markers of hemolysis
 - Increased lactate dehydrogenase (LDH)
 - Increased serum unconjugated bilirubin
 - Decreased haptoglobin
- Decreased serum B₁₂ and/or folate levels
- **Increased homocysteine or methylmalonic acid** are also evidence of B₁₂ deficiency

TREATMENT

MEDICATIONS

- **Supplementation:** increased dietary vitamin B₁₂ and/or folate when indicated
 - Parenteral vitamin B₁₂ if pernicious anemia
 - Dietary vitamin B₁₂ found in animal products
 - Folate found in both plant, animal products, esp. dark green leafy vegetables

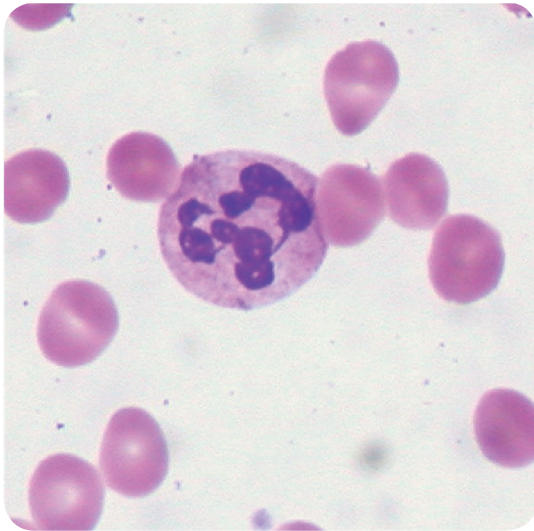


Figure 50.1 A hyperlobated neutrophil in a peripheral blood smear; a characteristic feature of megaloblastic anemia.

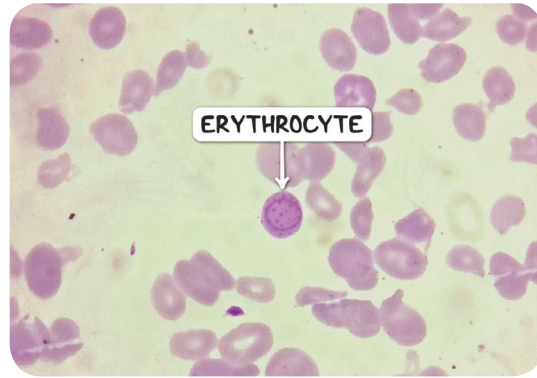


Figure 50.2 An erythrocyte displaying a Cabot ring and basophilic stippling. These features represent disordered erythropoiesis and are seen in many conditions, including megaloblastic anemias.

SIDEROBLASTIC ANEMIA

osms.it/sideroblastic-anemia

PATHOLOGY & CAUSES

- Anemias caused by altered mitochondrial function and defects in heme synthesis within erythroid cells

TYPES

Congenital forms

- Involve inheritance patterns affecting nuclear/mitochondrial genes encoding for erythrocyte synthesis—X-linked/autosomal recessive/mitochondrial inheritance patterns
 - **Syndromic:** presents with clinical manifestations of anemia along with effects on other organ systems (e.g. exocrine pancreatic insufficiency, sensorineural deafness, hepatic/renal failure, myopathy)
 - **Non-syndromic:** main features associated with anemia, iron overload

Acquired forms

- **Clonal:** myelodysplastic syndromes/ myeloproliferative neoplasms alter erythrocytes, granulocytes, platelets
- **Reversible (metabolic):** caused by exposure to a substance (e.g. excessive alcohol/drugs such as isoniazid, chloramphenicol; copper deficiency/zinc overload)

Both congenital & acquired

- **Impaired erythropoiesis, hemoglobin synthesis** → reduced iron in RBCs + defective RBCs undergo apoptosis within bone marrow + fewer functional RBCs in circulation → anemia
- **Circulating RBC morphology:** microcytic/ dimorphic (normocytic-to-macrocytic)

COMPLICATIONS

- Systemic effects of heme synthesis defects include impaired utilization of iron → accumulation in mitochondria → **systemic iron overload** → complications from hemochromatosis (e.g. diabetes, cardiac)

pathology)

- Repeated blood transfusions add to iron overload
- Anemia-induced acceleration of erythropoiesis → erythroid hyperplasia of bone marrow
- Increased risk of infection
- Acute leukemia develops in some cases
- Infection possibly fatal

SIGNS & SYMPTOMS

- Presentation variable depending on cause
- Clinical manifestations of decreased oxygen-carrying capacity of RBCs and hypoxia (e.g. fatigue, dyspnea, palpitations, pallor; mild jaundice if hemolysis significant)
- Erythropoietic hemochromatosis will manifest as varying degrees of iron overload (e.g. hepatosplenomegaly, cardiac arrhythmias, heart failure)

DIAGNOSIS

LAB RESULTS

Bone marrow aspirate smear

- Presence of sideroblasts confirms diagnosis
 - Prussian blue stain reveals iron ring around nucleus

RBC indices

- Low MCH
- MCV may be low/normal/high
 - Acquired sideroblastic anemias often produce macrocytic erythrocytes
 - Hereditary sideroblastic anemias produce microcytic erythrocytes

Blood smear analysis

- Anisocytosis
- Poikilocytosis
- Micro/macrocytosis
- Hypochromic erythrocytes
- Iron-containing inclusions (Pappenheimer bodies) may be present

Complete blood count

- Decreased serum hemoglobin
- Decreased RBC count
- Decreased/low reticulocyte count—related to ineffective erythropoiesis

Iron studies

- Hemochromatosis

Genetic testing

TREATMENT

- If sideroblastic anemia acquired, cause is reversible with treatment

MEDICATIONS

- X-linked sideroblastic anemia: vitamin B₆ (pyridoxine)

SURGERY

- Reduce organ damage secondary to iron overload
 - Mild anemia: therapeutic phlebotomy

OTHER INTERVENTIONS

- Reduce organ damage secondary to iron overload
 - Mild anemia: therapeutic phlebotomy
 - Chelation therapy (e.g. deferoxamine)

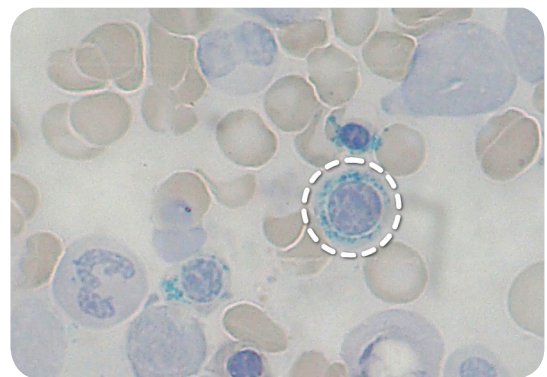


Figure 50.3 An erythrocyte displaying a Cabot ring and basophilic stippling. These features represent disordered erythropoiesis and are seen in many conditions, including megaloblastic anemias.